wherein

M is a transition metal ion;

the A-Y-B moiety is selected from the group consisting of -C≡C-, -CH=CH-, -N=N-, and -CH=N-;

X and X_1 are co-ligands and wherein at least one of X and X_1 is present; and,

Z is a phosphoramidite nucleotidyl moiety attached via the base.

REMARKS

Claims 44-49 are pending. An Appendix of Pending Claims is attached for the Examiner's convenience.

Claims 47 and 48 are objected to for informalities. Claims 44-49 remain rejected under 35 U.S.C. § 112, first paragraph for lack of enablement.

The following informalities have been objected to. First, in Claim 48, the Examiner requests that the misspelling of "isselected" be corrected. Applicants have amended Claim 48 to correct the misspelling of "isselected".

Second, in claim 47, the Examiner states that it is technically incorrect to have a nucleic acid moiety comprise a nucleic acid analog. The applicants respectfully disagree. As noted in the specification on page 11, lines 6-16, the term "nucleic acid" includes nucleic acid with analogous backbones, e.g. nucleic acid analogs. Thus, the Z moiety that comprises a nucleic acid moiety can comprise two nucleotides comprising a phosphodiester bond (page 11, line 8) or a phosphoramide bond (page 11, line 10), a peptide nucleic acid linkage (page 11, line 14), phosphorothioate (page 11, line 12), etc. Thus the term "nucleic acid moiety" includes "nucleic acid analog"; thus claim 47 is a correct dependent claim and both moieties are correct Z substituents. Accordingly, applicants request withdrawal of the objections.

Summary of The Rejections Under 35 U.S.C., §112, First and Second Paragraphs

In rejecting Claims 44-49 under 35 U.S.C. under § 112, first paragraph, the Examiner's has reiterated his position that the specification is entirely prospective. Specifically, the Examiner argues that the specification lacks specific embodiments which show the applicant had possession of the compounds indicated, that a substantial number of

compounds had been made, and that there is a complete absence of requisite guidance to permit the ordinary practitioner to make the compounds without undue experimentation.

It is well settled law that the specification must enable the scope of the claimed invention, but that the specification need not provide a specific description for each and every embodiment covered by the claimed invention. *See, e.g., Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991). That the claimed invention covers a wide variety of compounds amenable to synthesis in accordance with the claimed invention is not relevant to the issue of enablement. Rather, the test of enablement requires that the specification, in light of the prior art, provides ample guidance to one of skill in the art, to make and use the compounds of the invention. Applicants maintain that the specification provides specific examples of making at least two aromatic acetylene derivatives of phenanthroline. This alone is sufficient teaching to enable the scope of independent claims 44-46 and 48.

Synthesis of Aromatic Acetylene Derivatives of Phenanthrolines

To reiterate, the present invention is directed to the synthesis of 1,10-phenanthroline derivatives functionalized at the 3 and /or 8 positions. This is accomplished by the halogenation of 1,10-phenanthroline at the 3 and/or 8 positions. Once halognenated derivatives of 1,10-phenanthrolines are available, additional molecules can be added, such as transition metals, aromatic acetylenes, nucleic acids, nucelotides, nucleosides, proteins, etc.

The synthesis of aromatic acetylene derivatives of phenanthrolines requires: a) halogenation, particularly bromination, of 1,10-phenanthroline at the 3- and/or 8- position; b) optional addition of a transition metal to the halogenated 1,10-phenanthroline to form transition metal derivatives of 1,10 phenanthroline; and, c) palladium cross coupling to covalently attach acetylated aromatic compounds such as nucleic acids, nucleotides and nucleosides to the halogenated 1,10 phenanthroline (which may comprise transition metals).

Halogenation of 1,10-phenanthroline begins with commercially available 1,10-phenanthroline monohydrochloride monohydrate. A typical procedure using bromine is provided in working example 1. As outlined at page 23, lines 5-25:

> In a typical procedure, a solution of the 1,10-phenanthroline monohydrochloride monohydrate(10 g, 43 mmol) in nitrobenzene (20 ml) was heated to 130-140 °C in a 250 ml 3-neck flask. Bromine (3.3 l, 64 mmol in 9.3 ml nitrobenzene) was added dropwise over a period of 1 hr. Upon the

addition of bromine, the 1,10-phenanthroline went into solution. After stirring for 3 hr at the same temperature, the reaction mixture was cooled to room temperature, treated with concentrated ammonium hydroxide (100 ml) and extracted with dichloromethane (3X50 ml). The combined organic layers were washed with water (3X50 ml) and dried ($MgSO_4$). Concentration in vacuum afforded a suspension of the products in nitrobenzene. The nitrobenzene was removed by dissolving the suspension in dichloromethane (10 ml) and filtering it through silica gel (300 ml) using dichloromethane as the eluent. After the nitrobenzene eluted out, the products were recovered by gradually increasing the polarity of the eluent up to 10% MeOH in CH_2Cl_2. Flash column chromatography (0.6% MeOH in CH_2Cl_2) afforded 3-bromo-phenanthroline (3.6 g, 33% yield, m.p. 164-167°C) and the 3,8-bromo-phenanthroline (2.4 g, 17% yield, m.p. 270-273°C) as white powders. Higher solvent polarity (10% MeOH in CH_2Cl_2) elutes unreacted 1,10-phenanthroline (ca. 4 g) that can be recycled.

A typical reaction for adding transition metals to halogenated 1,10-phenanthrolines is described at page 27, lines 4-13:

> In a typical reaction, the ligand **3a** (0.1 g, 0.26 mmol) in degassed DMF (10 ml) was treated under argon with a solution of K_2RuCl_5 (33 mg, 0.08 mmol) in water (4 ml) containing 1 drop of 6N HCl. The solution was refluxed for 1 h. Sodium hypophosphite (38 mg, 0.44 mmol) in water (1 ml) was added, and reflux was continued for 1 h. After cooling to 60°C, the reaction mixture was treated with potassium hexafluorophosphate (48 mg, 0.26 mmol) as a 10% aqueous solution, cooled to RT and concentrated *in vacuo*. Silica-gel chromatography using 1% aqueous 0.5 M KNO_3 in acetonitrile as eluent afforded Ru(**3a**)$_3$. ^{1}H NMR (CD_3CN) d 8.75 (d, *J*=1.3 Hz, 2H, H2,9), 8.27 (s, 2H, H5,6), 8.18 (d, *J*=1.3 Hz, 2H, H4,7), 7.45 (m, 10H, phenyl).

Chemical compositions of ligand **3a** and Ru(**3a**)$_3$ are found in Tables 1 and 2 of the specification respectively.

With respect to the palladium-catalyzed coupling reactions, transition metal catalyzed reactions have played a role in organic synthesis for a long time. Over twenty five years ago the use of palladium as a catalyst for coupling reactions was disclosed. Since then, the scope of palladium-catalyzed reactions has been expanded and used to join a wide variety of chemical reactants via the formation of a carbon-carbon bond. See for example, U.S. Patent No. 6,136,157; a copy of which is attached as Exhibit A, which describes the efforts devoted to extending the scope of palladium-catalyzed reactions.

Briefly, palladium-catalyzed cross coupling reactions are used to form carbon-carbon bonds between halogenated carbons and other carbon atoms, such as alkynes, alkenes and aromatic acetylenes. This reaction is quite versatile and widely used to synthesize a large number of compounds. In particular, palladium-catalyzed cross coupling reactions have been used to couple nucleosides to a variety of compounds. For example, Robins and Barr report details of a high-yield palladium-catalyzed coupling procedure which provides direct access to 5-alkynyluracil bases and nucleosides from terminal alkynes and readily available 5-iodouracil derivatives. See Robins and Barr, (1983) *J. Org. Chem.*, 48:1854-1862, a copy of which is attached as Exhibit B. Moriarty et al. describe the use of a palladium catalyzed coupling reaction between 8-iodo derivatives of O-TBDMS protected adenosine, 2'-deoxyadenosine, and 2',3'-dedeoxyadenosine to obtain 8-substituted nucleosides. Moriarty, et al., (1990) *Tetrahedron Letters*, 41:5877-5880, a copy of which is attached as Exhibit C. Thus, the use of palladium catalyzed-cross coupling reactions in the coupling of nucleosides with other compounds is known in the art.

The present invention utilizes a palladium-catalyzed cross coupling reaction to make 1,10-phenanthrolines derivatives. Guidance for palladium-catalyzed cross coupling reactions between an aromatic acetylene and halogenated 1,10-phenanthroline is depicted in Scheme II, page 18 of the specification. Other palladium-catalyzed reactions include: a) reacting an halogenated 1,10-phenanthroline with acetylene, to form a 3- or 3,8-acetylene-phenanthroline and then coupling to an halogenated aromatic group (Scheme III, page 18 of the specification); b) coupling transition metal complexed 1,10-phenanthrolines with an aromatic acetylene (Scheme IV, page 20); c) coupling a transition metal complexed 3-acetylene phenanthroline with an aromatic bromine (Scheme V, page 20); and d) coupling an optionally transition metal complexed 1,10-phenanthroline with a halogenated nucleosides (page 20, line 8 through page 21, line 2).

Moreover, specific reaction conditions are disclosed in example 3, page 29, lines 17-24:

> A representative procedure for the palladium-mediated cross-coupling reactions between **4** and aromatic acetylenes is as follows. A mixture of **4** (50 mg, 0.052 mmol), $(Ph_3P)_2PdCl_2$ (4 mg, 0.0057 mmol) and CuI (0.5 mg, 0.0026 mmol) was treated with a degassed solution of 4-ethynyltoluene (11 µl, 0.11 mmol) in DMF (5 ml) and triethylamine (3 ml) for 1 hour at room temperature under Argon. The crude reaction mixture was evaporated to dryness and the

product **6** was obtained in 91% yield as an orange-red powder after successive crystallizations from dichloromethane-ethanol.

The chemical structures for compounds **4** and **6** are found on pages 31 and 32 respectively.

The substrates required for the palladium cross coupling reactions described in the present invention are widely available. Aromatic acetylenes can be made using techniques well known in the art or obtained commercially. See specification at page 20, lines 3-7. Halogenated bases and nucleosides are commercially available. *See* Robbins and Barr, Exhibit C. Moreover, halogenated bases and nucleosides can be synthesized using terminal alkynes and halogenated nculeosides as starting materials. *See* Moriarty et al., Exhibit B.

In further support of the enablement of the specification, applicants draw the Examiner's attention to a recent article which describes the synthesis of metal containing nucleosides. See Hurley and Tor (1998), *J. Am. Chem. Soc.*, 120:2194-2195, enclosed herein as Exhibit D. The applicants are not using subsequent work to supplement the disclosure of the application; rather, the subsequent work is presented to show that the utility asserted and shown in the application is supported by further research, and that the specification fully enables the synthesis of 1,10-phenanthroline derivatives substituted at the 3- and/8-positions. See In re Wilson, 135 USPQ 442, 444 (CCPA 1962); Ex parte Obukowicz, 27 USPQ 2d 1063 (BPAI 1993); Gould v. Quigg, 3 USPQ 2d 1302,1305 (Fed. Cir. 1987):

> "it is true that a later dated publication cannot supplement an insufficient disclosure in a prior dated application to render it enabling. In this case the later dated publication was not offered as evidence for this purpose. Rather, it was offered . . . as evidence that the disclosed device would have been operative."

Hurley and Tor report the synthesis of novel Ru^{II}- and Os^{II}-containing nucleosides and their phsophoramidite derivatives. The methods used to synthesis these metal-modified nucleosides are the same as those disclosed in the present invention and outlined above: a) halogenation of 1,10-phenanthrolines; b) the optional incorporation of transition metals to form transition methal complexed 1,10-phenanthroline derivatives, and, c) palladium-catalyzed cross coupling reactions between acetylated nucleosides and transition metal complexed 1,10-phenanthrolines. See Exhibit D, page 2194. In addition, the Hurley and Tor

reference utilize solid phase phosphoramidite chemistry to synthesize the corresponding metal-modified phosphoramidite. Exhibit D, page 2194; the specification, page 21, lines 1-2.

In further support of the proposition that the specification is enabling, the applicants submit the declaration of Dr. Tom Meade. Dr. Meade's declaration is enclosed as Exhibit 1.

In paragraph 7, Dr. Meade states that the bromination procedure used to make functionalized derivatives of 1,10 phenanthroline, is sufficiently described to allow one of skill in the art to make these compounds without undue experimentation.

Likewise, in paragraph 8, Dr. Meade states that the reaction described for adding the transition metal ruthenium to functionalized derivatives of 1,10 phenanthroline may be adapted for the addition of other metal ions without undue experimentation.

In paragraphs 9 and 10, Dr. Meade is of the opinion that sufficient guidance for using the palladium catalyzed cross coupling reaction to couple nucleosides to aromatic acetylene derivatives of 1,10 phenanthroline is provided in the specification.

In paragraph 11, Dr. Meade states that methods for synthesizing oligonucleotides are well known in the art. Moreover, Dr. Meade is of the opinion that the reference in the specification to the use of solid-phase phosphoramidite chemistry for the synthesis of the compounds of the present invention is sufficient to allow a person of skill in the art to make these compounds without undue experimentation.

Accordingly, in light of the prior art and teachings in the specification, applicants submit that the skilled artisan would find guidance for making the compounds described in the specification. Accordingly, applicants submit that Claims 44-49 are enabled and request withdrawal of the rejections under 35 U.S.C. § 112, first paragraph.

The Applicants submit that the claims are now in condition for allowance and an early notification of such is respectfully solicited.

Attached hereto is a marked-up version of the changes made to the claims by the "Restriction and Amendment". The attached page is captioned **"Version with markings to show changes made."**

The Commissioner is authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 06-1300 (our Order No. A-63463-1/RFT/RMS/RMK).

Dated: March 23, 01

Respectfully submitted,

FLEHR HOHBACH TEST
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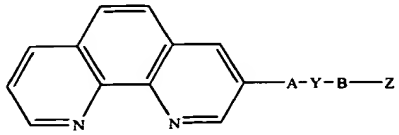
"VERSION WITH MARKINGS TO SHOW CHANGES MADE"

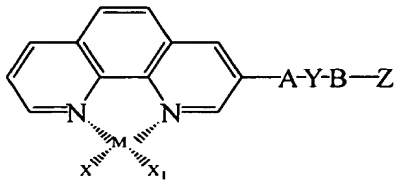
Claim 15 has been cancelled.

Claim 16 has been cancelled.

Claim 48 has been amended as follows:

48. (Thrice Amended) A compound represented by one of the formulae:

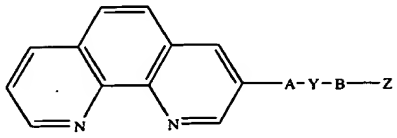


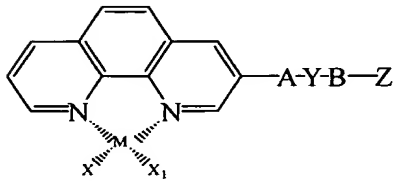


wherein
M is a transition metal ion;
the A-Y-B moiety [isselected] <u>is selected</u> from the group consisting of -C≡C-, -CH=CH-, -N=N-, and -CH=N-;
X and X_1 are co-ligands and wherein at least one of X and X_1 is present; and,
Z is a phosphoramidite nucleotidyl moiety attached via the base.

Appendix of Pending Claims

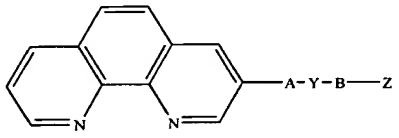
44. (Twice Amended) A compound represented by one of the formulae:

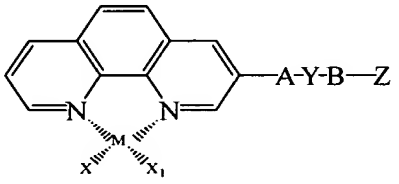




wherein
M is a transition metal ion;
the A-Y-B moiety is selected from the group consisting of -C≡C-, -CH=CH-, -N=N-, and -CH=N-;
X and X_1 are co-ligands and wherein at least one of X and X_1 is present; and
Z is a nucleosidyl moiety attached via the base.

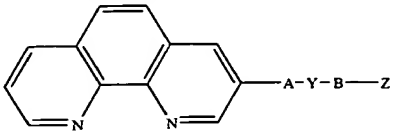
45. (Twice Amended) A compound represented by one of the formulae:

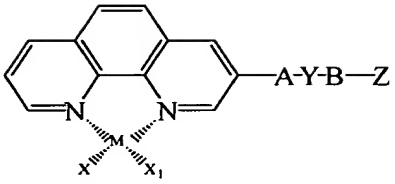




wherein
M is a transition metal ion;
the A-Y-B moiety is selected from the group consisting of -C≡C-, -CH=CH-, -N=N-, and -CH=N-;
X and X_1 are co-ligands and wherein at least one of X and X_1 is present; and
Z is a nucleotidyl moiety attached via the base.

46. (Twice Amended) A compound represented by one of the formulae:

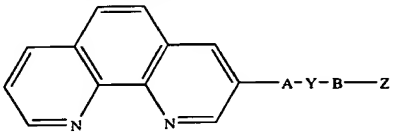


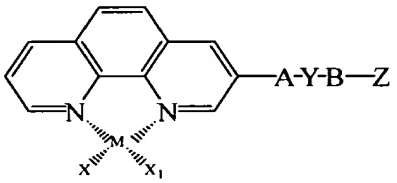


wherein
M is a transition metal ion;
the A-Y-B moiety is selected from the group consisting of -C≡C-, -CH=CH-, -N=N-, and -CH=N-;
X and X_1 are co-ligands and wherein at least one of X and X_1 is present; and,
Z is a nucleic acid moiety attached via a base.

47. A compound according to claim 46, wherein said nucleic acid moiety comprises a nucleic acid analog.

48. (Thrice Amended) A compound represented by one of the formulae:





wherein
M is a transition metal ion;
the A-Y-B moiety is selected from the group consisting of -C≡C-, -CH=CH-, -N=N-, and -CH=N-;
X and X_1 are co-ligands and wherein at least one of X and X_1 is present; and,
Z is a phosphoramidite nucleotidyl moiety attached via the base.

49. A compound according to claims 44, 45, 46 or 48 wherein M is selected from the group consisting of ruthenium, rhenium and osmium.